10/578043

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To: 12/5

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/052789	International filing date *(day/month/year)* 03.11.2004
Priority date *(day/month/year)* 03.11.2003	
International Patent Classification (IPC) or both national classification and IPC C12N5/06	
Applicant PROBIOGEN AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/052789

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-14
	No:	Claims	1-3
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents :

D1: KIM H ET AL: 'ALTERATIONS IN P53 AND E2F-1 FUNCTION COMMON TO IMMORTALIZED CHICKEN EMBRYO FIBROBLASTS' ONCOGENE, BASINGSTOKE, HANTS, GB, vol. 20, no. 21, 2001, pages 2671-2682, XP001157349 ISSN: 0950-9232

D2: BENNETT MARTIN R ET AL: 'Cooperative interactions between RB and p53 regulate cell proliferation, cell senescence, and apoptosis in human vascular smooth muscle cells from atherosclerotic plaques' CIRCULATION RESEARCH, vol. 82, no. 6, 6 April 1998 (1998-04-06), pages 704-712, XP002275529 ISSN: 0009-7330

D3: WAZER DAVID E ET AL: 'Immortalization of distinct human mammary epithelial cell types by human papilloma virus 16 E6 or E7' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 92, no. 9, 1995, pages 3687-3691, XP002275530 1995 ISSN: 0027-8424

D4: WILLIAMS BART O ET AL: 'Cooperative tumorigenic effects of germline mutations in Rb and p53' NATURE GENETICS, vol. 7, no. 4, 1994, pages 480-484, XP009028188 ISSN: 1061-4036

SECTION V

1.1 In the present set of claims, it should be render clear (Art.6 PCT) that the immortalized cell line which are claimed undergo this phenotype due to an active process of affecting cellular genes or transfecting the cells with viral genes, and not that the immortalized cell lines are affected in said pathways due to a standard processus of immortalization. In the absence of such further precision, an objection under novelty (Art.33(2) PCT) against claims 1-3 arises for the following reasons : D1 (see abstract) relates to immortalized chicken embryo fibroblast cell lines which have been established in continuous cell culture. The expression pattern of p53 and

E2F-1 has been tested, showing a down and up-regulation, respectively. The E2F-1 factor is known to be involved in the pRb pathway. Therefore, the cells of D1 fall into the scope of at least claim 1.
In addition, the cells of D1 are in the absence of contrary evidence, supposed to fall into the scope of claims 2-3 too.

1.2 Further objections under Art.6 in combination with Art.5 PCT arise with respect to claims 1-3 since the matter for which protection is sought is not clearly defined. The functional statements of affecting the function of the retinoblastoma and the p53 proteins (claim 1), overcoming G1 checkpoint control and preventing apoptosis induced by a gene (claim 2), mediating disruption of complexes between retinoblastoma proteins and E2F transcription factors, and preventing transcriptional activation by p53 (claim 3) do not enable the skilled person to determine which technical features are necessary to perform the stated functions.

2. Even rendered novel over D1 and clear and supported by the description, the present application does not meet the requirements of Art.33(3) PCT for the following reasons :

The subject-matter of the present application differs from the closest prior art D1 in that the immortalized cellular line is transformed with genes providing an alteration in the p53 and the pRb pathways. However, the authors of D1 (see p.2672, left-hand column, l.51-54) state that "the differential expression of both p53 and E2F-1 genes seem to be a common event in immortal CEF cells and could be an early event in the process of cellular immortalization" and that (see l.59) "such changes (induced by the alteration of p53 and E2F-1 expression) may be sufficient to extent cellular life-span similar to the life extension observed by the inactivation of both p53 and pRb via introduction of SV40 large antigen". In addition, the authors suggest to trigger "functional studies involving the down-regulation of p53 by expression of antisense p53 mRNA and up-regulation of E2F-1 by introduction of exogenous E2F-1" that could "help determine the direct relationship between genetic alterations of p53 and

E2F-1 and cellular immortalization". Thus, it clearly appears a skilled person in the art, starting from D1 would have easily envisaged that the p53 and E2F-1 genes having altered function may be directly responsible or at least involved in the process of immortalization in CEF cells, and then would have envisage to apply the knowledge from other prior art concerning p53 and pRb. In particular, it is well known that inactivation of both p53 and pRb pathways result in immortalization or transformation of human and mouse cells (see D2-D4). Thus, applying the same inactivation of both p53 and Rb pathways to the cells of D1, the skilled person in the art would have obviously arrived at the subject-matter of claim 1. The subject-matter of independent claims 9, 11, 12, 14 appears to be merely obvious derived method and uses.

Thus, the presence of an inventive activity in the present application is denied.

3. Further clarity objections are raised (Art.6 PCT):
The expressions and terms "or the like", "etc." render the scope for which protection is sought unclear.

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Anmeldung Nr:
Application no.: 03025158.1
Demande no:

Anmeldetag:
Date of filing: 03.11.03
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

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Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Immortalized avian cell lines for virus production

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C12N5/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PT RO SE SI SK TR LI